REMARKS/ARGUMENTS

This submission accompanies a Request for Continued Examination and addresses the issues presented in the Office Action of June 6, 2010, a Final Rejection.

In item 4 of the Office Action the Examiner responds to arguments submitted in response to the previous Office Action. The remaining items in the Office Action are a direct reproduction of the Examiner's objections in the previous Office Action. Despite applicants' comments, and the positive IPRP at the international stage on this application, the Examiner has maintained a rejection of claims 1-4, 7-9, 11-17 and 19-21 as lacking novelty over US 5,531,925 (Landh *et al.*), the only prior art document applied to the claims. The Examiner considers that the remaining claims (5, 6, 10 and 18) are obvious over this document.

The Action states that applicants' previous arguments have been considered fully, but only commented on one aspect of these. The Examiner has chosen to summarize the previous arguments as the assertion that there is no disclosure of a compound having a stipulated 1-10% range of anionic structure forming amphiphile or of the need for these to have particular non-polar groups (C6-C32 alkyl/alkenyl) or of the improvement in delivery cationic peptides.

The Examiner's response is simply to reiterate his previous assertions that Landh *et al* teaches the analogous composition comprising the analogous cationic peptide hormone, and that the disclosure of GMO containing 1% free fatty acids in which the fatty acid composition has C16-C18 and C20 encompasses the claimed C6-C32 alkyl/alkyenyl non-polar groups. This is not the case.

It seems that the Examiner is confusing the disclosure of 1% free fatty acids within GMO, i.e. that the GMO component contains a free fatty acid impurity, present in the maximum amount as 1% of the GMO itself, with a composition having an *overall* content of anionic structure forming amphiphile in the range of 1-10%. This is incorrect as explained in detail in the remarks that follow.

The Examiner has referred to specific compositions disclosed in column 11, lines 35 to 66 and column 17, line 35 of Landh *et al*. These are two GMO/poloxamer 407/water compositions and one GMO/SPC/poloxamer composition having relative proportions of 50/3.5/46.5 wt% and 6.5/4/89.5 wt%, and 6.5/3.5/1.0 wt% respectively. Clearly these compositions contain 50% GMO, or 6.5% GMO. Please note that when correctly calculated a

composition having an overall GMO content of 6.5 wt%, where the GMO itself contains 1% of free fatty acids, will contain an overall percentage of 0.065% free fatty acids. Likewise a composition containing 50% GMO will contain only 0.5% free fatty acids overall. Thus these compositions *cannot* contain the required 1% of anionic component due to this impurity.

GMO itself is not an anionic structure forming amphiphile but a neutral structure forming amphiphile. The only anionic amphiphile components disclosed in the compositions of Landh *et al* are the impurities present within GMO, i.e. the free fatty acids which comprise a maximum of *1% of the GMO component*. A composition containing 1% of anionic structure forming amphiphile, where this is derived solely from the 1% of impurities present in GMO, would have to be made up of 100% GMO. None of the compositions disclosed in Landh contain only GMO, i.e. are 100% GMO (otherwise they would be "GMO", not "compositions" according to the current application). Therefore it is *not possible* for the disclosed compositions of Landh *et al* to contain 1% of free fatty acids. Hence, the requirement of current claim 1 that a composition contains 1-10% anionic structure forming amphiphile level *cannot* be met by the disclosed compositions of Landh *et al*. or by any composition that could be reached by following the teaching of Landh.

As explained above, there is no disclosure within Landh *et al* of a composition which contains at least one anionic structure forming amphiphile in the required weight range of 1-10% and having non-polar groups selected from C6-C32 alkyl and alkenyl groups, as well as fulfilling all the other conditions of claim 1, specifically a cationic peptide active agent having an isoelectric point of above 7.0 and at least one neutral structure forming amphiphile, in addition to the requirement that the composition comprises a non-lamellar phase structure and/or forms a non-lamellar phase structure on exposure to body fluids.

For the reasons given above claim 1 is clearly novel over the disclosures of Landh *et al*, as correctly decided in the IPRP.

As mentioned previously, the remainder of the Office Action simply repeats the Examiner's points from his first Office Action. The previous comments are reiterated here.

Landh *et al*. is principally concerned with the formation of colloidal particles having an interior non-lamellar phase, and with processes for their formation. The majority of this document relates to the formation of GMO/water phases including GMO/fragmentation

agent/water, GMO/SPC/water, GMO/SPC/fragmentation agent/water and GMO/somatostatin/water systems.

The Examiner states that Landh *et al.* discloses:

- a cationic peptide active agent having an isoelectric point of above 7.0, since it discloses somatostatin (octreotide) having a solubility of 0.3 mg/ml, a net charge of 4 and a pI = 10 (col. 14, lines 15-25);

- a neutral structure forming amphiphile, since it discloses GMO (col. 5, line 15 and col. 14, lines 15-45);

- an anionic structure forming amphiphile having C_6-C_{32} alkyl and alkenyl non-polar groups and comprising a fatty acid, since it discloses GMO of which 1% is made up of fatty acids having a composition including C16, C18 and C20 groups, or SPC having C8, C12, C16, C18 groups (col. 11, lines 35-50), and amphiphilic polymers comprising anionic alkylsulfates, soaps and sulfosuccinates (col. 16, line 31);

- a non-lamellar phase structure, since the abstract discloses colloidal particles comprising an interior phase of a non-lamellar reversed cubic, hexagonal or intermediate phase, or an L3 phase.

However, in the context of Landh *et al.* these disclosures are isolated and relate to many different particle systems disclosed as separated embodiments in that application. As explained above, there is no disclosure of any composition which satisfies all of the conditions of current claim 1 even if all of the above are taken in combination. In particular, there is no disclosure of a composition having the stipulated 1-10 wt.% range of anionic structure forming amphiphile, or of the need for these to have particular non-polar groups (C_6-C_{32} alkyl/alkenyl), or of the effects which are to be achieved, i.e. the improvement in delivery of cationic peptides.

In view of the above, the only compositions disclosed in Landh *et al.* are outside the scope of current claim 1 because they do not contain an active agent and/or cannot contain the necessary amount of anionic structure forming amphiphile (see column 11, lines 50-66 and column 17, line 35). Current claim 1 and its dependent claims therefore cannot be anticipated by Landh *et al.*

It is clear, for the reasons given above, that current claim 1 is novel over Landh *et al.*

Turning to non-obviousness, the Examiner argues that Landh *et al.* teaches towards the current invention. In fact, however, Landh *et al.* is directed to the provision of small particles of amphiphile-based solvent systems for drug delivery and other applications. The solution to this problem is a method of fragmentation which provides dispersed particles of non-lamellar phases in solvents such as water.

Landh *et al* is silent with regard to the problem addressed by the present application, the improvement in delivery of *cationic peptides*, particularly for oral and depot administration, which is achieved in the present case by the recognition that the *inclusion of an anionic lipid component* improves the drug load, delivery and in particular the protection of the peptide from the endogenous peptidase activity present throughout the body. It has been demonstrated that the anionic components are critical to the slow-release behavior of the present compositions and that the use of such simple anionic lipids as those now recited overcomes the problem that certain sterol-type anionic components disrupt the non-lamellar phase behavior. These are problems which are not recognized or addressed in Landh *et al.* It is notable that this key aspect of including an anionic lipid component, from which the advantage of the present invention is derived, is the one aspect of the claim not mentioned by the Examiner in section 4. This is because Landh *et al.* does not consider such a component. It also demonstrates that Landh does not provide teaching that could render the present claim obvious.

The Examiner is of the view that it would be obvious to achieve the claimed features of each of claims 5, 6, 10 and 18 but unfortunately does not indicate *how* such features could be achieved. The answer, however, is to include an anionic lipid component in an amount sufficient to achieve these goals. This is limited to 1 to 10%, which is a level that would not be achieved by the inclusion of incidental impurities. There is no teaching prior to the present application which could lead a skilled worker to use an anionic amphiphile in order to achieve these results. The only anionic components in Landh are present as unwanted impurities at a level below that currently claimed. Following the prior art thus cannot result in compositions of the claimed invention and the present claims cannot therefore be obvious over Landh *et al.* or any of the cited art.

Since there is no discussion in Landh *et al* of the problems addressed by the current application, it seems fanciful to suggest that this document can teach the skilled man the claimed

solution. No incentive is provided to modify Landh *et al.* in order to actively add an anionic component and thus to develop the composition of claim 1. Furthermore, no advantage of the use of an anionic lipid component is suggested.

As recognized by the International Examiner, the effects discussed above are not taught towards by the cited art, and indeed, the prior art Chang *et al.* (D5 in the ISR) indicates that no advantage would be derived, thus entirely missing the effects such as peptidase protection now presented by the inventors, and teaching directly away from the present invention.

Reconsideration and favorable action are solicited.

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 14-1140.

Respectfully submitted,

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